REMARKS

Claims 81, 82, 85, 86, 102, 124, and 144-150 are currently under consideration in the instant application. Claim 150 has been amended. Claims 151-156 have been added. Support for the amendment to the claims can be found in the specification and claims as filed, as discussed below. Claims 144-146 have been cancelled without prejudice. No new matter has been added.

Rejection of Claims Under 35 USC 112, First Paragraph

The Examiner has indicated that he believes that there is no support for the single-chain TCR language in claim 81 disclosing "α and β variable chain TCR covalently linked together by a second peptide linker". In addition to the other portions of the specification noted in the prior response to Office Action, Applicants respectfully point to paragraph 78 of the application as published (page 20, line lines 4-5) recites "Alternatively, linker sequence may be linked to both α and β chains of the TCR molecule." providing for support for the claim language.

Further, Applicant points to the specification in the paragraph bridging pages 8 and 9 in which International application WO 99/18129, originally referred to in the specification as US Application Serial No. 08/943,086, which claims priority to the US application, is incorporated by reference. Applicant has copied text, specifically from page 4, lines 13-17, into the instant specification. The MPEP provides for incorporation of text from a reference that was incorporated by reference into the application as filed.

> 2163.07(b) Incorporation by Reference [R-3]
>
> Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter.

Therefore, the added text should not constitute new matter, and clearly supports an scTCR comprised of a TCR Vα and Vβ chain in the absence of a constant domain.

The Office Action asserts that there is no support for claims 144-146. Applicant respectfully disagrees, however, to progress the prosecution of the application, Applicant has cancelled claims 144-146.

The Office Action asserts that there is no support for the limitations of claims 147-149 as the specification is stated to not support a first linker sequence and a second linker sequence. Applicant respectfully disagrees and points to the language from the specification supporting claim 81 which clearly recites two linker sequences. Support for a linker between an alpha and beta chain of a TCR is provided in paragraph 78 of the application as published (page 20, lines 4-5 of the application as filed) and in the single-chain TCR linker language of application 08/943,086 as described above. Additionally, specific examples of a linker, e.g. (G4S)4, between the alpha and beta variable chains of the TCR are provided in Figure 1a, Example 1 (page 31 lines 14-18) and Example 2 (page 32 lines 7-9). As acknowledge by the Examiner, the specification also discloses linkers between the TCR and biologically active molecule (e.g., page 15, lines 6-8). Support for the specific linker sequence lengths in both claims 147 and 148, and in new claims 151 and 152 is provided in paragraph 78 of the application as published (page 19, lines 23-24 of the application as filed). The ability of the linker to provide flexibility is discussed in the same paragraph (e.g., page 19, line 29-30page 20, lines 13-14).

Based on the foregoing, Applicants believe that there is support in the specification for the claims as pending. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejections.

Rejection of Claims Under 35 USC 103

The Examiner rejected the pending claims under 35 USC 103(a) as being unpatentable over Weidanz et al. in view of Bonneville et al. and as being unpatentable over Weidanz et al. in view of Bonneville et al. and further in view of Theobald et al. Applicants traverse this rejection.

In the prior response to Office Action, Applicant provided a Declaration by one of the inventors demonstrating the surprising results obtained using the fusion molecules of the instant invention. The Office Action does not give full consideration to the Declaration and alleges that

> there is no disclosure in said declaration of the actual structure of the constructs used or how they were made. Thus, it is unclear as to whether said constructs are encompassed by the claims under consideration and it is unclear if said constructs were made using methods disclosed in the specification.

Applicant points to the Declaration which states in paragraph 6 that

> The results below indicate that the IL-2 domain of the **claimed fusion molecules** (c264scTCR/IL-2 and MART-1scTCR/IL2) exhibit longer cell surface residency time and bind more stably to the IL-2 receptor than does IL-2 when not a part of the claimed fusion molecules. [emphasis added]

Therefore, from the Declaration itself, it is clear that the c264scTCR/IL-2 and MART-1scTCR/IL2 fusion molecules are the claimed fusion molecules. The specification routinely uses the term "scTCR" as soluble chain TCR, and IL-2 is also used throughout the specification and understood. The response to the Office Action also notes that the experiments in the Declaration are carried out using the "claimed fusion molecules" (page 20). The basic structure of the fusion molecules used in the experiments performed in the Declaration is TCR V-alpha -- linker -- TCR V-beta -- TCR C-beta -- linker -- IL-2". This clearly falls within the scope of the molecules of claims 81 and 153; therefore, the Declaration should be given full weight and consideration by the Examiner.

Applicant notes that the claims are directed to compositions, not methods. The methods of making the claimed compositions used in the Declaration need not be the same as those provided in the specification. There can be no requirement that the Declaration include methods of making the fusion molecules assayed.

The Declaration and the specification provide **objective evidence** of non-obviousness that must be considered by the Examiner as noted in MPEP 716.01(a).

> Affidavits or declarations>, when timely presented,< containing evidence of criticality or unexpected results... **must be considered by the examiner** in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103....

> **Examiners must consider comparative data** in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims. *In re Margolis*, 785 F.2d 1029, 228 USPQ 940 (Fed. Cir. 1986). The lack of objective evidence of nonobviousness does not weigh in favor of obviousness. *Miles Labs. Inc. v. Shandon Inc.*, 997 F.2d 870, 878, 27 USPQ2d 1123, 1129 (Fed. Cir. 1993), cert. denied, 127 L. Ed. 232 (1994).

Further, MPEP section 716.02(a)(III) sets forth they type of surprising results, such as those provided in the Declaration and the specification, can provide evidence of non-obviousness.

III. < PRESENCE OF AN UNEXPECTED PROPERTY IS EVIDENCE OF NONOBVIOUSNESS

> Presence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound); *Ex parte Thumm*, 132 USPQ 66 (Bd. App. 1961)

It could not be expected from the teachings of the cited art that fusion of an scTCR to IL-2 would substantially improve the pharmacokinetic properties of IL-2, e.g. by substantially increasing the half-life of IL-2, without disrupting IL-2 activity.

Further, the knowledge of those of skill in the art would suggest that fusion of a peptide to either the C-terminus or the N-terminus of IL-2 with a peptide linker would disrupt the function of the cytokine. For example, the abstract from Ju et al. (1987 *J. Biol. Chem.* 262:5723, copy enclosed) states:

> Our analysis of over 50 different mutations demonstrated that the integrity of **at least three regions of the IL-2 molecule is required for full biological activity: the NH_2 terminus (residues 1-20),** the COOH terminus (residues 121-133), and 2 of the 3 cysteine residues (58 and 105). Deletion of the NH_2-terminal 20 amino acids or the COOH-terminal 10 amino acids resulted in the loss of greater than 99% of bioactivity and binding. **Amino acid substitutions at specific positions in these regions also resulted in proteins which retained less than 1% activity.**

As amino acid substitutions can result in the IL-2 protein retaining less than 1% of its activity, it would be expected that fusion of a large peptide, e.g., an scTCR, would result in the inactivation or at least substantial loss of activity of IL-2. Applicant submits that the simple

knowledge of the existence of the various claimed components would not be sufficient to assemble the components into the instantly claimed molecule.

The issue of obviousness in chemical cases has been reviewed by the Courts in view of the recent KSR decision.

> "While the KSR Court rejected a rigid application of the . . . TSM test in an obviousness inquiry, the Court acknowledged the **importance of identifying 'a reason** that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination."
>
> "When there is a design need or market pressure to solve a problem and there is a finite number of **identified, predictable solutions**, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. * * * That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. **Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound**." *Takeda Chemical Industries Ltd. v. Alphapharm Pty*. 492 F.3d 1350 (Fed. Cir. 2007) [emphasis added]

Applicant submits that the importance of the N-terminus of IL-2 for the functioning of IL-2 would have directed one of ordinary skill in the art away from fusion of a large peptide to the N-terminus of IL-2.

The *KSR* decision does not abrogate the need for some suggestion in the reference or in the art to modify a particular reference in a particular manner. The cited references provide no motivation to modify the references to arrive at the instantly claimed invention.

The claims are directed to soluble single-chain T cell receptor fusion molecules comprising a T cell receptor and a cytokine or fragment thereof connected by a first peptide linker, wherein the soluble single-chain T cell receptor has one recognition binding site and the cytokine or fragment thereof has a different recognition binding site, wherein the soluble single-chain T cell receptor comprises α and β variable chain TCR, wherein the α and β variable chains are covalently linked together, optionally by a second peptide linker.

Specifically, Weidanz et al. teach that a soluble single chain TCR comprising an effector molecule linked to the single chain TCR via an Ig-C_L chain. Weidanz et al. teach that the

effector molecule can be a cell toxin or biologically active fragment thereof, a chemotherapeutic drug or a detectably-labeled radionuclide molecule suitable for diagnostic or imaging studies (Weidanz page 32 line 32 to page 33 line 19). Weidanz et al. do not teach that the effector molecule is a cytokine. Additionally, the effector molecules taught by Weidanz et al. are structurally and functionally very different than a cytokine molecule. It is unpredictable whether a cytokine domain will fold correctly as part of a TCR fusion molecule such that it retains receptor binding capability. For example, the effector molecules taught by Weidanz et al. do not recognize receptors on the surface of effector cells in order to mediate their activities.

Weidanz et al. teach a Ig-C_L chain linking the effector molecule and the TCR. The Ig-C_L chain (or functional fragment) between about 70 to 150, preferably between about 90 to 120, and more preferably between about 100 to 110 amino acids in length (Weidanz page 18 lines 23 to 25). In contrast the current application disclose a peptide linker between the single-chain TCR and the cytokine wherein the peptide linker is preferably from about 7 to 20 amino acids, more preferably from about 8 to 16 amino acids (page 19 lines 23-24). Applicant has added claims 151 and 152 to clearly recite that the length of the linker consists of the specific number of amino acids recited. Thus the structure of the peptide liker of the current application and the linking Ig-C_L chain of Weidanz are different. (Although not cited by the Examiner, Weidanz does disclose linking the TCR and effector molecule with a second linker.)

Bonneville teaches soluble heterodimeric (two chain) T cell receptors (T receptors) comprising VαCα and VβCβ subunits or other combinations of Vγ-Cγ and Vδ-Cδ subunits (column 2 line 39 to column 3 line 6). Bonneville does not teach a single-chain T cell receptor. Bonneville also teaches a fusion protein between a soluble T receptor and a peptide sequence, the peptide sequence being constitutive of a peptide or of a protein, the fusion protein is obtained by fusing DNA sequence encoding the peptide or protein to one of the chains or to the two chains of DNA encoding the subunits of a T receptor from which their transmembrane portions has been deleted, followed by a co-transfection of the DNA sequences thus fused into a host cell (column 3 line 42 to 50). Bonneville teaches that the peptide sequence is IL-2 (column 3 lines 52-53). Thus, Bonneville teaches a soluble heterodimeric (two-chain) TCR directly fused to one or two IL-2 proteins without a peptide liker between the TCR subunits that the IL-2 protein. However, Bonneville only provides these protein complexes as constructs that could be made. There are no data demonstrating that the TCR-IL-2 fusion protein complexes were ever made or

tested to determine if the expressed constructs folded properly or had any of the desired activities.

In contrast the claimed TCR fusion protein comprises a single-chain TCR fused to a cytokine with a peptide linker that allows effective positioning of the biologically active molecule with respect to the TCR molecule binding groove so that the T cell receptor can recognize presenting MHC-peptide complexes and the biologically active molecule can modulate the activity of a cell either to induce or to inhibit T-cell proliferation, or to initiate or inhibit an immune response to a particular site (page 15 lines 6-18). Therefore, the claimed TCR fusion protein and that taught by Bonneville differ in structure in several respects: 1) Bonneville's TCR domain is a **two-chain construct** comprising two TCR variable-constant domain chains whereas the TCR domain of the invention is a **single chain construct** comprising a Vα chain linked to a Vβ chain and 2) Bonneville's **IL-2 domain is fused directly to the TCR** domain whereas the cytokine domain of the invention is **linked to the TCR domain by a linker** sequence that allows effective positional of the two domains to permit functional activity.

Bonneville does not specifically exemplify the construction or characterization of soluble TCR proteins comprising a fused IL-2 domain. In addition, Bonneville does not disclose any functional activity of the fused IL-2 domain in the TCR fusion protein. The Examiner states that IL-2 is specific for recognition of effector cells (immune cells expressing IL-2 receptors such a activated T cells). However, **Bonneville does not teach that the IL-2 domain of the TCR fusion protein retains this or any of the other known biological activities of IL-2.** Given that the IL-2 domain is fused directly to the TCR domains in the constructs of Bonneville, it is uncertain whether the IL-2 domain is capable of binding IL-2 receptor expressed on immune cells due to changes in the fused IL-2 domain structure or steric hindrance by the adjacent TCR domains. As it was known that both the N-terminal and C-terminal domains of IL-2 are important for its biological activity (see for example, Ju et al. 1987. *J. Biol. Chem.* 262:5723), **one skilled in the art would expect that the IL-2 domain of Bonneville directly fused to either the C-terminus or N-terminus of the TCR chain(s) would not retain biological activity.**

In contrast, the claimed soluble TCR fusion protein comprising a fused biologically active cytokine is specific for recognition of an effector cells and can modulate the activity of a

cell either to induce or to inhibit cell proliferation, or to initiate or inhibit an immune response (claim 86, page 15 lines 6-18, page 19 lines 14-21). Construction, production and characterization of such TCR fusion proteins are shown in Examples 5 - 11, 15 and 16. For example, the biological activity of the fused IL-2 domain of the invention to induce cell proliferation of an IL-2 dependent T cell line is demonstrated in Example 9.

Combining the teachings of Weidanz et al. with Bonneville would not lead to the claimed invention. As indicated, the structure of the TCR fusions of Weidanz et al. and Bonneville are different from each other and from the TCR fusions of the invention. For example, neither Weidanz et al. nor Bonneville disclose a peptide linker between a single-chain T cell receptor and a cytokine that effectively positions these domains such that the T cell receptor can recognize presenting MHC-peptide complexes and the cytokine can recognize immune effector cells. In addition, there is a complete lack of disclosure by both Weidanz et al. and Bonneville as to the functional activity of the cytokine domain of the TCR fusion molecule that is provided in the claimed invention.

Moreover, the claimed molecules have a number of beneficial characteristics that were unexpected and that are not taught or suggested by the cited references alone or in combination. Submitted herewith is a declaration by Hing Wong, Ph.D., an inventor of the instant application and the President and CEO of Altor Bioscience Corporation detailing the unexpected and surprising results demonstrated by the claimed molecules. For convenience, the contents of the declaration will be summarized below.

The Declaration sets forth a number of experiments that show, unexpectedly, that the claimed fusion molecules have highly enhanced efficacy when compared to the any portion of the molecules alone. Specifically, the claimed fusion molecules exhibit longer cell surface residency time and bind more stably to their cell surface receptors than do the cell surface ligands when not part of the fusion molecules. Specifically, the declaration sets forth data demonstrating that the claimed fusion molecules (c264scTCR/IL-2 and MART-1scTCR/IL-2) exhibit longer cell surface residency time and bind more stably to the IL-2 receptor than does IL-2 when not part of the claimed fusion molecules. The experiments further demonstrate that the claimed molecules, (264scTCR/IL-2 and MART-1scTCR/IL-2) showed equivalent IL-2 biologic activity *in vitro* and *in vivo*.

The declaration also details a set of experiments that demonstrate that scTCR/IL-2 fusion proteins unexpectedly have a much longer serum half-live and higher serum recovery than rhIL-2 alone. **The longer half-life, modest tissue distribution, slow clearance and stable bifunctionality of the scTCR/IL-2 fusion proteins provide significantly more favorable pharmacokinetic properties than are observed for IL-2-based therapeutic agents.**

The experiments described above, and detailed in the previously filed Declaration, result in unexpectedly enhanced efficacy of the claimed molecules. For example, the data in the Declaration demonstrates that the claimed scTCR/IL-2 fusion proteins have significantly greater efficacy against well-established human xenograft tumors than does rhIL-2 alone. Specifically, treatment with 264scTCR/IL-2 led to marked inhibition of tumor growth and partial to complete regression of tumors in mice by the completion of the dosing regimen, while tumors in mice administered rhIL-2 alone continued to grow at a rapid rate increasing over 4 fold during the course of treatment.

Accordingly, based on the arguments submitted above, and the experiments detailed in the Declaration, the pending claims would not have been obvious to one of skill in the art at the time of filing the instant application. Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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